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Original article

Effects of exercise on symptoms of anxiety in primary care patients: A randomized controlled trial

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ABSTRACT

Background: There is a need for high-quality research regarding exercise interventions for persons with anxiety disorders. We investigate whether a 12-week exercise intervention, with different intensities, could reduce anxiety symptoms in patients with anxiety disorders.
Methods: 286 patients were recruited from primary care in Sweden. Severity of symptoms was self-assessed using the Beck Anxiety Inventory (BAI) and the Montgomery Åsberg Depression Rating Scale (MADRS-S). Participants were randomly assigned to one of two group exercise programs with cardiorespiratory and resistance training and one control/standard treatment non-exercise group, with 1:1:1 allocation.
Results: Patients in both exercise groups showed larger improvements in both anxiety and depressive symptoms compared to the control group. No differences in effect sizes were found between the two groups. To study a clinically relevant improvement, BAI and MADRS-S were dichotomized with the mean change in the control group as reference. In adjusted models the odds ratio for improved symptoms of anxiety after low-intensity training was 3.62 (CI 1.34–9.76) and after moderate/high intensity 4.88 (CI 1.66–14.39), for depressive symptoms 4.96 (CI 1.81–13.6) and 4.36 (CI 1.57–12.08) respectively. There was a significant intensity trend for improvement in anxiety symptoms.
Limitations: The use of self-rating measures which bears the risk of an under- or overestimation of symptoms.
Conclusions: A 12-week group exercise program proved effective for patients with anxiety syndromes in primary care. These findings strengthen the view of physical exercise as an effective treatment and could be more frequently made available in clinical practice for persons with anxiety issues.

1. Introduction

Today's standard treatments for anxiety are cognitive-behavioral therapy (CBT) and pharmacological treatment. Despite notable pharmacological advances, treatment resistance, side-effects (Garakani et al., 2020; Ravindran and Stein, 2010) and poor medication adherence

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(Ashton, 2005; Solmi et al., 2021) are common among patients with anxiety disorders. Furthermore, long waiting lists for CBT may worsen symptoms and long-term prognosis. General practitioners (GPs) within primary health care need treatments that are personalized, non-stigmatizing, low on side-effects and easily prescribed.

One such treatment is physical activity, which can be used alone or in combination with standard treatments. There is empirical support for the role of exercise, defined as structured physical activity aiming to increase or maintain fitness, as a treatment and protection against depression (Conn, 2010; Danielsson et al., 2014). A meta-analysis of randomized controlled trials (RCTs) concluded that exercise is an effective intervention for reducing symptoms of depression (Kvam et al., 2016) and prospective meta-analysis demonstrated that higher levels of physical activity reduce the risk of depression (Schuch et al., 2018). Concerning treatment for anxiety, the literature is conflicting. The authors of a recent meta-review based on meta-analyses of RCTs concluded that the evidence for exercise as treatment for anxiety disorders is equivocal (Ashdown-Franks et al., 2020). For example, two included meta-analyses showed effectiveness of aerobic exercise compared to non-active control (Aylett et al., 2018; Stubbs et al., 2017), but no superiority to standard treatments was also reported (Bartley et al., 2013). Only one meta-analysis (Aylett et al., 2018) compared high-intensity exercise with low-intensity showing superiority for high-intensity exercise. Several of the interventions included in the meta-review were at high risk of bias due to low power, short follow-up time and inadequately controlled RCTs (Ashdown-Franks et al., 2020; Bartley et al., 2013). Moreover, research on different types of exercise and dose-responses is sparse and interventional studies have rarely been conclusive (Jayakody, 2014; Lucibello, 2020; Wipfli, 2008). There is clearly a need for high-quality RCTs and effective exercise treatment protocols for patients with anxiety disorders.

The primary aim of the current study was to investigate the effects of an exercise intervention on symptoms of anxiety and to evaluate the benefit of moderate/high intensity exercise vs low intensity exercise, in primary care patients diagnosed with anxiety disorder. A secondary aim was to evaluate change in depressive symptoms. Another secondary aim was to study mediating effects of cardiovascular fitness on anxiety symptoms. Our primary hypothesis was that a 12-week exercise intervention would reduce symptoms of anxiety and that this effect would be larger for moderate/high-intensity exercise than for low-intensity. Secondly, we hypothesized that exercise would also improve depressive symptoms.

2. Material and methods

2.1. Participants and randomization procedure

Participants for this study originate from the randomized, parallel, controlled clinical intervention study Swedish Physical Fitness and Brain - Interventional Study (PHYSBI; NCT03247270;Trial Registration Date: 08/08/2017), aiming to investigate effects of an exercise intervention for patients with anxiety disorders in the primary care setting. Procedures are detailed in our study protocol (Nyberg et al., 2019). Briefly, individuals presenting with symptoms of anxiety were recruited by a GP or psychologist. Participants included were informed both verbally and in writing, thereafter they signed a written informed consent. At baseline assessment, the study physician assessed information about physical co-morbidities and the study psychiatrist diagnosed anxiety disorders and psychiatric comorbidities such as major depression (confounder in statistical regression models) using the Mini International Neuropsychiatric Interview (M.I.N.I; Swedish version 6 and 7.0.0) a structured diagnostic interview with high reliability and validity (Sheehan et al., 1998). Included in the study were patients aged 18 - 65 diagnosed with anxiety disorders using Diagnostic and Statistical manual of Mental disorders (DSM-IV and V), including panic disorder (PD; DSM 300.01), generalized anxiety disorder (GAD; DSM 300.02) and anxiety not otherwise specified (NOS; DSM 300.00). Patients with primary diagnoses social phobia and agoraphobia were not included due to the situational nature of anxiety in these conditions, as well as the fact that CBT provides a viable treatment option. Patients with and without ongoing treatment with psychoactive medication (antidepressants or anxiolytics) were included; medication modification was allowed during the study period. Individuals with ongoing psychotherapy were not included. An exclusion criterion was baseline physical exercise level exceeding one exercise occasion per week during the last three months. Additional exclusion criteria were a pathological ECG (electrocardiogram), pregnancy, use of beta-blocker, previous serious mental illness (psychotic disorder and bipolar disorder), ongoing severe substance or alcohol abuse syndrome and ongoing burn-out syndrome as well as elevated suicide risk as assessed by the GP. For further details, please see the study protocol (Nyberg et al., 2019).

Following the baseline assessment, the study physiotherapists randomized, coded and pseudonymized the participants into three groups with 1:1:1 allocation, using computer generated randomization (http://www.randomizer.org). All researchers who were involved in data assessments, except the physiotherapists who delivered the exercise interventions, were blinded to group allocations. For half of the included patients, training intensity group was only blind to the study researchers, while patients were aware of the treatment group. For the other half, participation in low- vs. moderate/high-intensity training group was double-blinded to both study researchers and patients. All personnel in the study used the term intervention/exercise in communication with other personnel and patients, irrespective of training intensity group. Furthermore, the intervention group's exercises took place at different time points, reducing the risk of intensity comparisons by the participants. 12-weeks assessment were collected by personnel not involved in any data analyses. Comparison of these two study halves enable us to determine if the blinding procedure reduced result bias. The study was approved by the regional Ethics Committee in the Gothenburg, Sweden, National Board of Health (300–16). The study was carried out in accordance with the latest version of the Declaration of Helsinki.

2.2. Measures

2.2.1. Primary and secondary outcomes

Primary outcome was self-assessed severity of perceived anxiety symptoms using the clinically well-established psychiatric assessment scale Beck Anxiety Inventory (BAI) ©2005 by NCS Pearson (Beck and Epstein, 1988). BAI mainly evaluates somatic symptoms (tremor, experience of palpitations etc.); it was developed to be relatively free from depressive content (Beck and Epstein, 1988). It is organized in 21 items, with scoring from nothing (0 p), slightly (1 p), moderately (2p) and severely (3p) and total ratings range from nothing, minimal/mild (score 0–15), moderately (score 16–25) and severely (score 26–63). Both reliability (Beck, 2001) and validity (Kohn and Beck, 2008) are reported to be high. Severity of ongoing symptoms of depression (secondary outcome) was self-assessed using the Montgomery Åsberg Depression Rating Scale (MADRS-S) (Montgomery and Asberg, 1979) (Svanborg and Asberg, 1994). Ratings were divided in no/minimal depression (score 0–12), mild (score 13–19) and moderate (score 20–34). We also analyzed question 2 in the MADRS-S as it provides a rating of anxiety (inner tension).

2.2.2. Measured baseline variables

Cardiorespiratory fitness/maximal oxygen uptake capacity (VO_2max) and muscle strength were measured using standardized tests according to the study protocol (Nyberg et al., 2019).

Blood pressure, weight and height were measured, and body mass index (BMI) was calculated for each patient. Alcohol use was assessed using the Alcohol Use Disorders Identification Test (AUDIT) (Saunders and Grant, 1993).

2.2.3. Self-reported baseline variables

In a questionnaire designed by the research team (Nyberg et al., 2019), patients self-reported education, marital status, years with anxiety issues, current sick-leave, use of psychoactive (anti-depressants or anxiolytics) prescription drugs (including dosage and duration at each assessment), smoking (yes or no), comorbidities (physical and psychiatric diagnoses) and physical exercise (occasions and minutes).

2.3. Intervention

Patients were randomized to one of three groups: 1) Intervention I: 12-week group exercise program with low-intensity training 3 times per week; 2) Intervention II: 12-week group exercise program with moderate to high-intensity training 3 times per week; 3) Control group: a single session with a physiotherapist who provided general advice about physical activity according to public health recommendations and, after study completion, a 3-month membership at a fitness facility. Participants were discouraged of actuating other exercise programs during the trial.

The intervention was carried out at a fitness facility in Gothenburg and both intervention I and II included similar cardiorespiratory and resistance training exercises, but at different intensities. A pulse-watch and the Borg RPE scale were used to monitor level of exertion to ensure appropriate exercise intensity. Low intensity was defined as 1.5 – 2.9 metabolic equivalents (METs), a Borg rated perceived exertion (RPE) of 10–14 and 40–59% of maximal heart rate and moderate/high intensity as 3.0–8.9 METs, Borg RPE 12–17 and 60–94% of maximal heart rate. The exercise program was designed as a circuit training with 12 stations, repeated twice. Cardiorespiratory exercises included step-ups, lunges, jump rope, burpees, step touches side-to-side and step-touches on step boards. Resistance training exercises included squats, abdominal plank position, hip lifts, crunches, row exercises and push-ups. The training session lasted for one hour per occasion including 10 min of warm-up exercises and 5 min of cool-down and stretching. A registered physiotherapist from primary health care rehabilitation designed individualized programs during a single one-on-one session with the patients. The intervention groups then exercised in separate sessions under the guidance of the physiotherapist who attended all exercise sessions and registered attendance. Participants in intervention II were encouraged to perform an additional running session per week. Patients unable to participate in a session performed replacement exercises on their own.

Two adverse events associated with exercise participation that required intervention and medical care were reported: 1) one patient in the high intensity group developed symptoms of fatigue and exhaustion disorder during intervention and 2) one participant had a spinal disk herniation at L5-S1when lifting a bench shortly after a training session. After the first event a baseline screening with a self-assessed instrument for exhaustion disorder (Karolinska Exhaustion Disorder Scale (Besèr et al., 2014)) was added in the autumn of 2019. The second event was not considered preventable and elicited no change in the study protocol.

2.4. Statistical analysis

A statistician performed a statistical power analysis prior to the study initiation (Nyberg et al., 2019). In order to achieve an adequate number of study participants, to allow for expected drop-outs, we recruited 25% more subjects than required. All statistical analyses were performed using SPSS version 25 software (SPSS Inc., Armonk, New York). Normality was assessed graphically using plotted histograms, and data were presented as means and standard deviations (SD) or 95% confidence intervals (CI) if normally distributed, otherwise as medians and interquartile ranges (IQR).

Changes between baseline and post-treatment were presented as means with corresponding CIs. Descriptive data were assessed at baseline using Chi-square for proportions and the Mann Whitney U or Kruskal Wallis tests for non-parametric or skewed distributions. For correlation analysis, we used the non-parametric Spearmanńs rank correlation and the parametric Pearsońs correlation, as indicated by rho values (r) and p-values.

Our main outcome variables were primary changes in BAI and secondary changes in MADRS-S. In order to assess the overall effectiveness i.e. effect size of the two intervention groups vs. the control group, we used analysis of covariance (ANCOVA) in a general linear model, generating a standardized mean difference.

Further, BAI and MADRS-S were dichotomized with the mean change in the control group as reference. Thus, we defined improvement in anxiety symptoms as a between-group difference (improvement) of 5 points on the BAI scale, based on the mean difference in BAI scores between baseline and week 12 for the control group. The rationale for using this cut-off limit for improvement was also based on our original sample size calculation in which an effect size of 0.5 difference between groups was deemed clinically relevant (Shiranibidabadi and Mehryar, 2015; Usmani et al., 2017). For depression symptoms, we used a cut-off difference (improvement) of 3 points on MADRS-S, which corresponds to the mean improvement of the control group. These dichotomies were then used for binary logistic regression with multivariable adjustments in various models of confounding. These were model 1: age and sex (Stubbs et al., 2017); model 2: model 1 with the addition of baseline psychoactive medication (Bandelow et al., 2015), major depression and BAI-score (Cohen et al., 2015); model 3: model 2 in addition to adding also baseline cardiovascular (Roest et al., 2010) and respiratory disorders and smoking (Cohen et al., 2015); model 4: model 3 in addition to baseline physical exercise (number of occasions and minutes per week). The odds ratios (OR) are presented with each intensity as a categorical factor and with both intensities as a continuous parameter, thereby showing "P-trend". A significant P-trend indicates a gradual increase in ORs for each of the higher intensities (from control to low, from low to high intensity).

For mediator analysis of changes in cardiorespiratory fitness and muscle strength on the observed effects of exercise on anxiety and depressive symptoms (score improvements from baseline to post-treatment, delta-values), we used correlation matrices and multivariable binary regression analyses. These were performed with treatment group (control, low- and high intensity) and changes in cardiorespiratory fitness and muscle strength as independent variables and BAI and MADRS-S scores as dependent variables, with adjustment as in model 3 (described above).

A p-value below 0.05 was considered statistically significant for all analyses.

3. Results

3.1. Participants characteristics

The flow of patients through the trial is summarized in Fig. 1. In total, 286 individuals agreed to participate and conducted baseline assessment. After exclusions (n = 29) and withdrawals (n = 34), 223 individuals were randomized and allocated to one of three groups. Baseline characteristics of the study sample are shown in Table 1. Mean age for both genders was 38.6 years and the majority were women (70%). The most common anxiety disorder was GAD (57.5%) followed by PD (46.4%). Psychiatric comorbidities were common. Cardiorespiratory fitness was considerably lower compared to the Swedish population (Ekblom-Bak et al., 2019), BMI indicated overweight, and 15% reported daily tobacco use. Participants had a higher proportion of hazardous alcohol use according to AUDIT than the national average (Källmén, 2019). Approximately half of the participants had lived with anxiety more than 10 years at baseline. At baseline, 27% were on sick leave and almost two thirds (63.5%) were on at least one psychoactive medication. This medication was initiated during the past month in 6.8%, and a similar proportion started treatment with antidepressants or

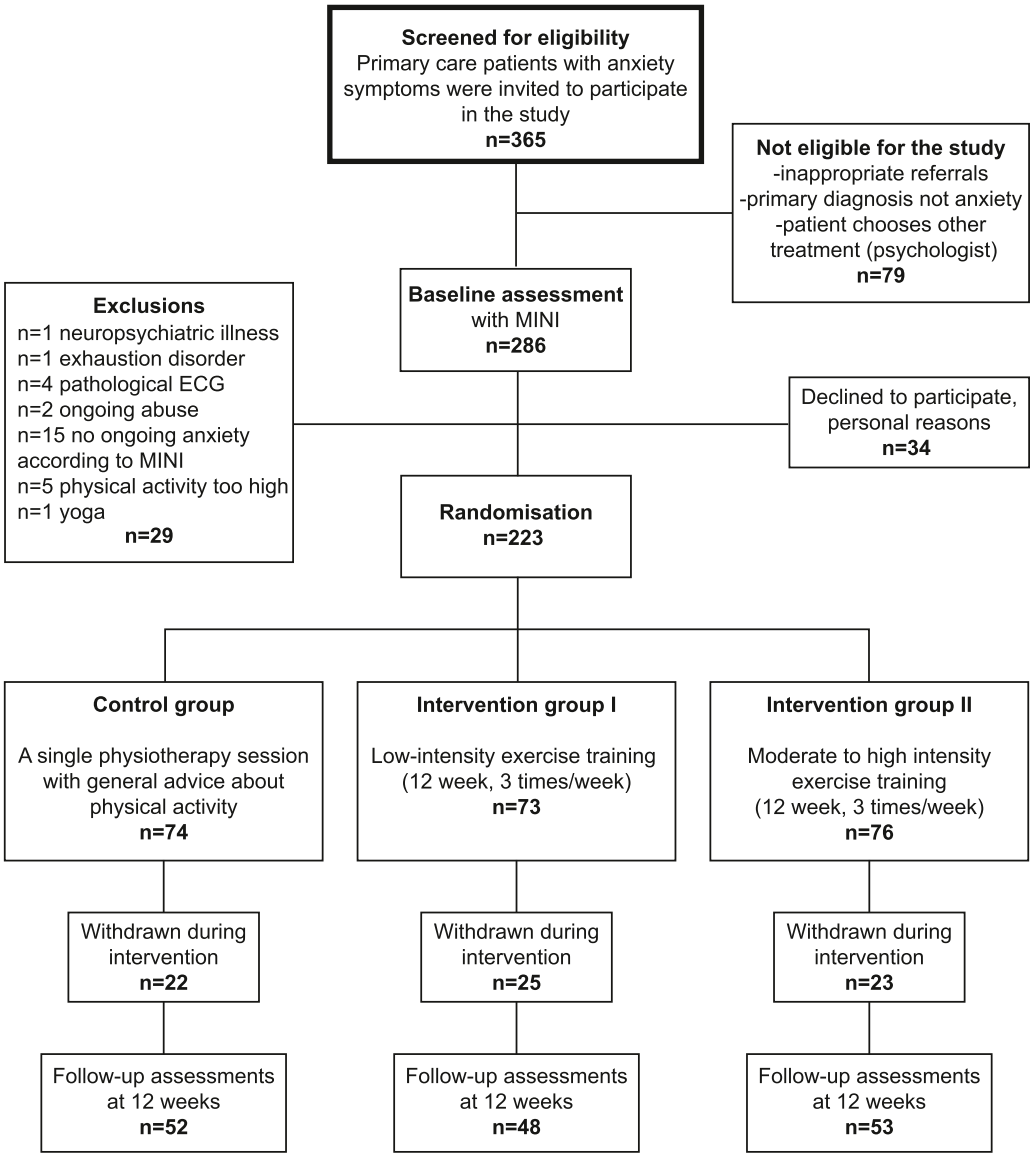

Fig. 1. Participant flowchart across the study.
Abbreviations: ECG, electrocardiogram; MINI, Mini International Neuropsychiatric Interview Swedish version 6 and 7.0.0 DSM-IV and V.

anxiolytics during the trial. A dosage reduction of antidepressants or anxiolytics was recorded for 11.5% at some point during the intervention; dosage was increased in 8.1%.

3.2. Primary outcome

A significant reduction in anxiety from baseline to post-treatment was observed in both treatment groups compared to the control group. Effect sizes are shown in Fig. 2a. Fully adjusted models did not attenuate the effects (Supplementary Table 2). Although BAI scores in all three groups decreased from baseline to post-treatment (Fig. 2b and Supplementary Table 1), the mean reduction was greater by approximately 5 points in both low and moderate/high-intensity exercise groups compared to the control group (Fig. 2b). While anxiety levels in most participants corresponded to moderate to severe anxiety at baseline (BAI scores between 23.8 and 25 points), anxiety levels at follow-up corresponded to mild anxiety in both exercise groups. Level of inner tension (MADRS-S item 2) was lower at follow-up in the moderate/high-intensity exercise group compared to the control group. The difference in the low intensity group compared to the control group was significant only in the fully adjusted model (Supplementary Table 2).

Descriptive frequencies for the dichotomized BAI variable (improvement/no improvement) are shown in Table 2. In fully adjusted models the OR for improved symptoms of anxiety for low-intensity exercise was 3.62 (CI 1.34–9.76) and for moderate/high intensity 4.88 (CI 1.66–14.39) (Table 3). Including both intensities as a continuous parameter revealed a significant intensity trend ($p = 0.003$ in the fully adjusted model). OR for improved inner tension (MADRS-S item 2) after low intensity exercise compared to the control group was 2.21 (CI 0.92–5.3) in fully adjusted model, and after moderate/high intensity exercise 4.21 (CI 1.61–11.02) (Table 3). Including both intensities as a continuous parameter showed a significant intensity trend ($p = 0.003$ in a fully adjusted model).

3.3. Secondary outcome

Both exercise interventions also significantly reduced the level of depression compared to the control group (Fig. 2a and Supplementary Table 2). Mean MADRS-S scores decreased in all three groups (Fig. 2c and Supplementary Table 1), but both exercise intervention groups

Table 1
Descriptive characteristics and exercise group comparisons at baseline assessment.

Characteristic	Controlgroup		Low intensity group		Moderate/ High intensity group		p-value
	Mean [SD] or n (%)	n	Mean [SD] or n (%)	n	Mean [SD] or n (%)	n	
Age (years)	37.9 [10.9]	52	38.3 [12.3]	48	39.6 [11.6]	53	0.69
Men/Women	17/35 (32.7/ 67.3)	52	13/35 (27.1/ 72.9)	48	16/37 (30.2/ 69.8)	53	0.83
Marital status							0.44
Unmarried	29 (55.8)	52	28 (58.3)	48	36 (70.6)	51	
Married	16 (30.8)	52	16 (33.3)	48	13 (25.5)	51	
Divorced	6 (11.5)	52	4 (8.3)	48	1 (2.0)	51	
Widow/ Widower	1 (1.9)	52	0 (0)	48	1 (2.0)	51	
Education above high school	33 (63.5)	52	25 (53.2)	47	30 (56.6)	53	0.57
BMI (kg/m^2)	27.2 [5.1]	52	27.1 [6.0]	48	27.4 [5.1]	53	0.88
Systolic pressure (mm/Hg)	122.6 [13.0]	50	120.6 [10.9]	43	124.8 [15.8]	50	0.32
Diastolic pressure (mm/Hg)	74.58 [9.7]	50	75.0 [9.3]	43	78.2 [11.8]	50	0.24
Smoking	7 (13.5)	52	9 (18.8)	48	7 (13.5)	52	0.70
Years with anxiety							0.55
<1 year	8 (15.7)	51	10 (21.7)	46	5 (10.2)	49	
1–10 years	14 (27.5)	51	13 (28.3)	46	18 (36.7)	49	
>10 years	29 (56.9)	51	23 (50)	46	26 (53.1)	49	
Psychoactive medication	33 (63.5)	52	31 (64.6)	48	33 (62.3)	53	0.97
Antidepressants	27 (51.9)	52	22 (45.8)	48	28 (52.8)	53	0.75
Anxiolytics	13 (25)	52	15 (31.3)	48	11 (20.8)	53	0.48
Physical exercise (occasions/ week)	0.37 [0.67]	51	0.44 [0.79]	47	0.76 [0.97]	51	0.05
Physical exercise (min/week)	18.46 [38.4]	52	31.0 [96.0]	47	37.2 [56.4]	51	0.07
Cardiorespiratory fitness (ml/ kg*min)	30.4 [9.4]	51	29.9 [9.2]	48	30.1 [8.3]	52	0.92
Muscle strength (right leg)	16.4 [11.1]	51	15.0 [10.2]	45	14.3 [8.6]	45	0.78
Muscle strength (left leg)	15.2 [10.8]	51	14.6 [9.8]	45	14.3 [9.1]	45	0.94
Rating scale scores							
BAI	24.8 [13.2]	52	25 [11.7]	48	23.8 [12.6]	53	0.84
MADRS-S	21.5 [8.3]	52	22.9 [8.1]	48	19.8 [7.7]	53	0.21
MADRS-S q. 2 (inner tension)	3.2 [1.3]	52	3.5 [1.1]	48	3.3 [1.0]	53	0.85
AUDIT	4.6 [5.31]	52	4.1 [3.4]	48	5.2 [5.4]	53	0.81
Anxiety diagnoses[a]							
Panic disorder	27 (51.9)	52	20 (41.7)	48	24 (45.3)	53	0.58
GAD	34 (65.4)	52	27 (56.3)	48	27 (50.9)	53	0.32
Anxiety NOS	6 (11.5)	52	9 (18.8)	48	10 (18.9)	53	0.52
Comorbidities[a]		52		48		53	0.48
Major depression	19 (36.5)		21 (43.8)		17 [32.1]		
Suicidality	11 (21.2)	52	12 (25)	48	11 (20.8)	53	0.85
Social phobia	29 (55.8)	52	17 (35.4)	48	22 (41.5)	53	0.11
Agoraphobia	21 (40.4)	52	14 (29.2)	48	13 (24.5)	53	0.20
PTSD	6 (11.5)	52	5 (10.4)	48	3 (5.7)	53	0.54
Alcohol use syndrome	6 (11.5)	52	4 (8.3)	48	7 (13.2)	53	0.73
Substance use syndrome	2 (3.8)	52	0 (0)	48	0 (0)	53	0.14
Personality syndrome	6 (11.5)	52	2 (4.2)	48	4 (7.5)	53	0.39
OCD	7 (13.5)	52	2 (4.2)	48	5 (9.4)	53	0.27
Bulimia nervosa	2 (3.8)	52	3 (6.3)	48	3 (5.7)	53	0.85
Cardiovascular disorder	0 (0)	52	4 (8.3)	48	6 (11.5)	52	0.05
Respiratory disease	3 (5.8)	52	1 (2.1)	48	5 (9.6)	53	0.28

Abbreviations: AUDIT, Alcohol Use Disorder Identification Test; BAI, Beck Anxiety Inventory; BMI, Body Mass Index; GAD, Generalized Anxiety Disorder; MADRS-S, Montgomery Åsberg Depression Rating Scale Self-rated; MADRS-S q.2, question 2 on Montgomery Åsberg Depression Rating Scale Self-rated; NOS, Not Other Specified; OCD, Obsessive Compulsive Disorder; PTSD, Post-Traumatic Stress Disorder; SD, Standard Deviation. P-values are shown for the comparison between the three groups, and were obtained using Chi-square for proportions and the Mann Whitney U or Kruskal Wallis tests for non-parametric or skewed distributions.

[a] Diagnoses according to Mini International Neuropsychiatric Interview (MINI).

decreased on average approximately 5 points more than the control group (Fig 2c). Descriptive frequencies for the dichotomized MADRS-S variable (improvement/no improvement) are shown in Table 2. In the final multivariate model (Table 3), the low exercise intervention was associated with a more than five-fold increase in the odds of symptom improvement compared to the control group. A four-fold increase was observed for the moderate-high intensity group.

3.4. Variables post-intervention

The mean improvement in cardiorespiratory fitness level post intervention was 1.84 ml/kg*min in the control group; 2.09 ml/kg*min in low intensity group and 3.2 ml/kg*min in the moderate/high intensity exercise group (all non-significant). Mean muscle strength increased significantly, $p = 0.026$ for the low intensity group and $p = 0.006$ for the moderate/high intensity group, compared to control (low exercise group: from 15 to 19.5 on right leg and 14.6 to 19 on left; moderate/high exercise group: from 14.3 to 18 on right leg and 14.3 to 18.9 on left); (control group: from 16.4 to 17.1 on right leg and 15.2 to 16.6 on left).

3.5. Mediation analyses

Changes in cardiorespiratory fitness (VO_2max) or muscle strength did not significantly correlate with changes in anxiety or depressive symptoms. In multivariable binary regression analyses changes in VO_2max or muscle strength from baseline to post-treatment revealed no

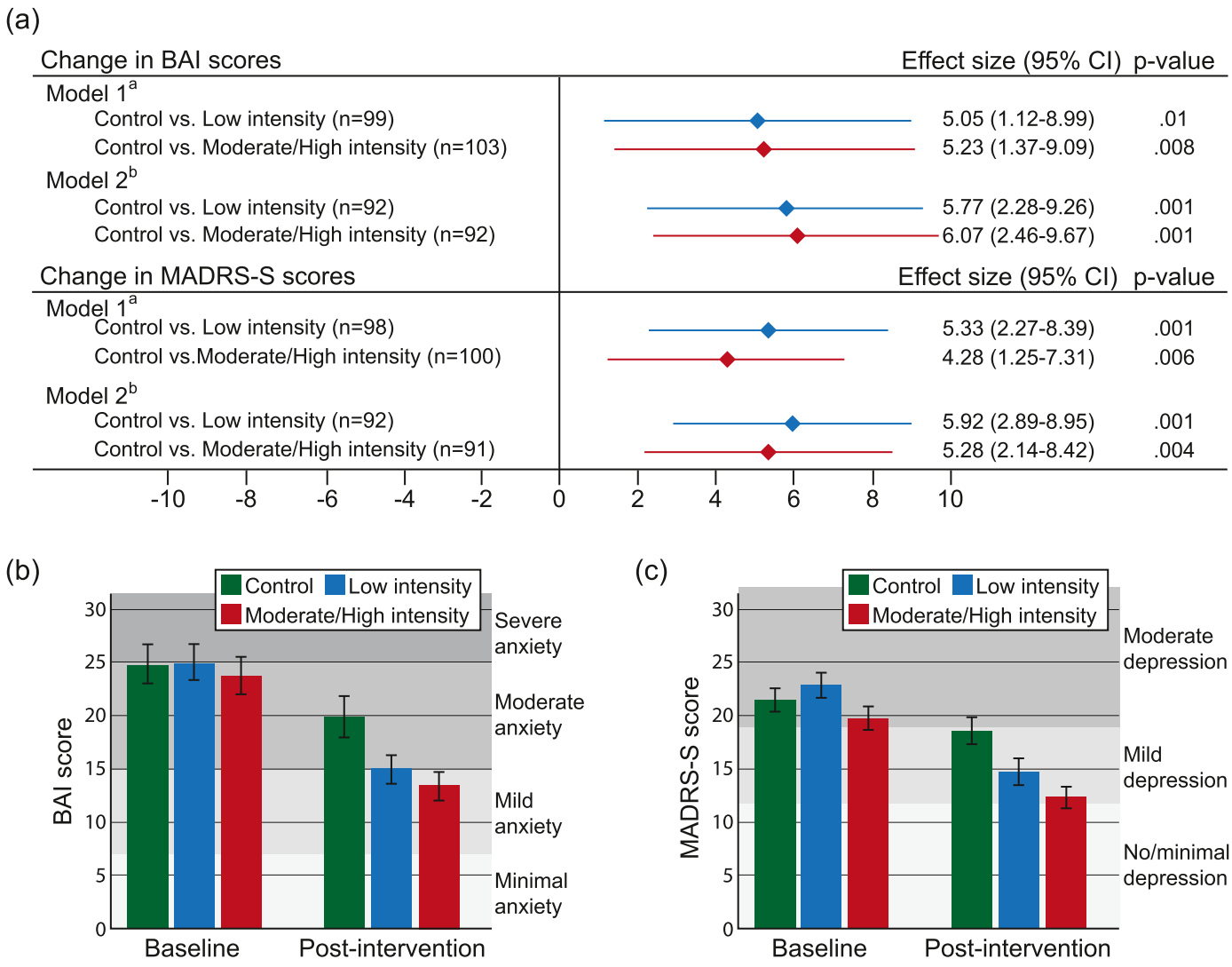

Fig. 2. Between-group treatment effects on self-rated anxiety symptoms (BAI scores) and depression symptoms (MADRS-S scores) (a). Both Low and Moderate/High intensity exercise training resulted in an average of approximately 5 points greater decrease in both the BAI and MADRS-S scores, compared to control treatment. Effect sizes were accessed using analysis of covariance (ANCOVA) in a general linear model, see Methods. Mean BAI (b) and MADRS-S (c) scores at baseline and at post-intervention by exercise intervention group. Error bars show standard error of the estimated means. Severity levels for anxiety (b) minimal/mild (score 0–15), moderately (score 16–25) and severely (score 26–63) and for depression (c) no/minimal (score 0–12), mild (score 13–19) and moderate (score 20–34) are indicated in shades of gray.

Abbreviations: BAI, Beck Anxiety Inventory Scale; CI, Confidence Interval; MADRS-S, Montgomery Åsberg Depression Rating Scale Self-rated

[a] Adjusted for sex and age

[b] Adjusted for sex, age and baseline psychoactive medication, major depression, BAI-score, cardiovascular and respiratory disorders, smoking and physical exercise at baseline.

significant mediation effects (data not shown).

3.6. Sensitivity analyses

Sensitivity analyses for the models described above for both primary and secondary outcomes in which participants who had started a pharmacotherapy during the intervention period ($n = 10$) were excluded did not affect the results (data not shown).

Odds ratios for improved symptoms of anxiety, inner tension and depression after exercise intervention programs, including only individuals who participated >50% of total sessions ($n = 85$), showed that the improvement for the low intensity group decreased and odds ratios for the high intensity group increased in adjusted models 1–3 (see Supplementary Table 3). These attenuations were not seen in model 4 (when including adjustment for physical exercise at baseline).

3.7. Adherence

Individuals in both exercise groups completed on average 25 sessions out of the total 36 sessions, which gives an adherence rate of 70%. Patients were reassessed after 12 weeks (response rate 69% including controls). The drop-out frequency was similar in all three groups (Fig. 1). However, a drop-out analysis revealed that the control group participants who discontinued had higher BAI scores and poorer cardiorespiratory fitness at baseline compared with individuals who dropped out in the exercise groups (BAI score on average 4.9 points higher and fitness 4.7 ml/kg*min lower).

3.8. Bias

Stratification for the two blinding procedures revealed stronger differences in treatment effects for the double-blinded ($n = 96$) compared

Table 2
Proportions of patients with anxiety disorders with or without improvements in anxiety and depression symptoms after a 12-week exercise intervention, by exercise intensity group.

	Non-exercise control	Low Intensity	Moderate/High intensity
BAI scores			
All, n	51	48	52
[a]Improvement, n (%)	22 (43.1)	32 (66.7)	34 (65.4)
No improvement, n (%)	29 (56.9)	16 (33.3)	18 (34.6)
MADRS-S scores			
All, N	50	48	50
[b]Improvement, n (%)	24 (48)	37 (77.1)	35 (70)
No improvement, n (%)	26 (52)	11 (22.9)	15 (30)

Abbreviations: BAI, Beck Anxiety Inventory Scale; MADRS-S, Montgomery Åsberg Depression Rating Scale Self-rated.

[a] Improvement in anxiety symptoms defined as an decrease in BAI scores of >5 points.

[b] Improvement in depression symptoms defined as an decrease in MADRS-S scores of >3 points.

For statistical evaluation regarding effects of intervention, see Table 3.

to the partly blinded ($n = 55$) procedure for both primary and secondary outcomes (data not shown), thus no indication of bias due to initial lack of blinding.

4. Discussion

This parallel RCT study of primary care patients with anxiety disorders supports an exercise intensity trend for improved anxiety symptoms but does not indicate large differences in effect sizes between low and higher intensities.

The present study shows that both low- and moderate/high intensity exercise interventions improved anxiety symptoms at follow-up. These effects were independent of depressive symptoms, which is important to assess given the well-known benefits of exercise for patients with major depressive disorder (Kvam et al., 2016; Rimer et al., 2012). Although no clear dose-response effect of exercise intensity was observed, there was a significant trend in the proportion of patients with improved anxiety symptoms with increased exercise intensity.

Our findings that no clear dose-response effect of exercise intensity was observed contrasts with findings presented in the review of Aylett et al. (2018). A partial explanation for the discrepancy might be related to that many persons in our study cohort had long histories of anxiety disorders and low physical activity at baseline. Hence, even the low intensity program resulted for most participants in a significant increase in physical activity compared to their previously sedentary lifestyles. The control group also improved their cardiorespiratory fitness, suggesting an increased physical activity as part of study participation, which could indicate an underestimation of the effect size.

We hypothesized that changes in cardiorespiratory fitness and/or muscle strength would predict anxiety outcomes. However, changes in VO2max or muscle strength from baseline to post-treatment revealed no significant mediation effects. To date, only one previous trial has addressed the link between changes in maximal oxygen uptake capacity (VO_2max) and clinical symptoms in anxiety disorders (Plag et al., 2020), reporting no correlations. Our results, taken together with those of others (Gordon and Herring, 2017, 2020; Rahman et al., 2018) suggest that improvements in strength are not required for mental health benefits in persons with anxiety syndromes. Several potential mechanisms may explain the effects of exercise on anxiety symptoms. First, the social participation in a group context with a supporting physiotherapist could be therapeutic in itself. The regular sessions per se might be one explanation for the symptom reduction. Almost one third of the participants in the present study were on sick-leave and regular meetings with others probably had a beneficial effect in this group. Secondly, neurobiological theories include systems involved in both how anxiety develops, and how physical activity affects the brain (Dishman et al., 2006). For example, exercise per se may stimulate production of

Table 3
Odds ratios for improved symptoms of anxiety, inner tension and depression after exercise intervention programs as compared to a non-exercise control group with the BAI and MADRS-S scores dichotomized with the median change in the control group as reference.

	Model 1[a] OR(95% CI)	p(n)	Model 2[b] OR(95% CI)	p(n)	Model 3[c] OR(95% CI)	p(n)	Model 4[d] OR(95% CI)	p(n)
BAI scores								
Low intensity	2.61 (1.15–5.91)	.02 (151)	3.33 (1.31–8.47)	.01 (150)	3.42 (1.33–8.81)	.01 (148)	3.62 (1.34–9.76)	.011 (136)
Moderate/High intensity	2.48 (1.12–5.51)	.03 (151)	3.61 (1.42–9.18)	.007 (150)	3.91 (1.48–10.3)	.006 (148)	4.88 (1.66–14.39)	.004 (136)
P-trend, both intensities	1.59 (1.06–2.38)	.03 (151)	1.9 (1.19–3.04)	.007 (150)	1.99 (1.22–3.23)	.006 (148)	2.29 (1.33–3.94)	.003 (136)
MADRS-S q.2 score (inner tension)								
Low intensity	1.57 (0.70–3.53)	.03 (149)	1.65 (0.72–3.74)	.24 (148)	1.73 (0.76–3.98)	.20 (146)	2.21 (0.92–5.3)	.074 (136)
Moderate/High intensity	2.26 (1.01–5.09)	.05 (149)	2.45 (1.07–5.62)	.003 (148)	2.81 (1.18–6.69)	.002 (146)	4.21 (1.61–11.02)	.003 (136)
P-trend, both intensities	1.51 (1.00–2.26)	.05 (149)	1.57 (1.04–2.37)	.003 (148)	1.68 (1.09–2.59)	.002 (146)	2.06 (1.28–3.33)	.003 (136)
MADRS-S scores								
Low intensity	3.65 (1.52–8.81)	.004 (148)	3.98 (1.58–10.04)	.003 (147)	4.57 (1.77–11.83)	.002 (145)	4.96 (1.81–13.6)	.002 (135)
Moderate/High intensity	2.6 (1.13–5.98)	.02 (148)	2.75 (1.16–6.54)	.02 (147)	3.20 (1.28–8.02)	.01 (145)	4.36 (1.57–12.08)	.005 (135)

Abbreviations: BAI, Beck Anxiety Inventory Scale; CI, Confidence Interval; MADRS-S, Montgomery Åsberg Depression Rating Scale Self-rated; MADRS-S q.2, question 2 on Montgomery Åsberg Depression Rating Scale Self-rated; OR, Odds Ratios. ORs were calculated using binary logistic regression with multivariable adjustments according to the models below. ORs are shown with each intensity as a categorical factor or with both intensities as a continuous parameter, thereby showing "P-trend". For MADRS-S p-trend analysis was not applicable, as this outcome did not show a linear dose-response.

[a] Adjusted for sex and age.

[b] Adjusted for sex, age and baseline psychoactive medication, major depression and BAI-score at baseline.

[c] Adjusted for sex, age and baseline psychoactive medication, major depression, BAI-score at baseline, cardiovascular and respiratory disorders and smoking.

[d] Adjusted for sex, age and baseline psychoactive medication, major depression, BAI-score at baseline, cardiovascular and respiratory disorders, smoking and physical exercise at baseline.

insulin-like growth factor 1 (IGF-1), which is associated with neuroplasticity and reduced anxiety-like behavior in mice (Ding et al., 2006). More research is needed regarding the specific underlying mechanisms that may explain how exercise can reduce symptoms of anxiety.

Recent findings indicate that anxiety could be an independent risk factor for cardiovascular disease (Karlsen et al., 2021), which further strengthens the use of exercise as treatment for patients with anxiety disorders. The understanding of these mechanisms has been explored in recent years and there are two main suggested pathways: a behavioral pathway (such as lower physical activity, smoking, alcohol consumption and poor diet) and a biological pathway (linking atherosclerosis to chronic inflammation) (Karlsen et al., 2021).

The current study has several strengths - a double-blinded design, baseline assessment randomization, adjustment of analyses for many potential confounders, sufficient statistical power and comparisons of two exercise intensities. The number of participants ($n = 153$) in our study is large in relation to previous RCT's on exercise in the treatment of anxiety disorder (Aylett et al., 2018; Gordon, 2020; Plag et al., 2020; Stubbs et al., 2017). Our adherence rate of 70% was good, especially considering the relatively long duration of our RCT. Although similar or higher adherence rates have been reported for some RCTs they involved shorter intervention times (Gordon, 2020; Plag et al., 2020). We also adjusted for potential confounders as well as considered cardiorespiratory and muscle strength as potential mediators in our statistical analyses. Another strength is that we addressed the overall risk of bias by repeating all analyses and comparing the treatment effects in single-blinded and double-blinded participants respectively. Results did not indicate bias.

There are also limitations. As mentioned above, participants in the exercise interventions groups may have benefited from time with attention and social interaction provided by the physiotherapist and other group members (Bartley et al., 2013) and a time-matched, active control group might have been more suitable. Drop-out analyses revealed that participants from the control group had higher anxiety ratings and lower cardiovascular fitness at baseline, which however would impact the results towards lower effect sizes. Another limitation is the use of self-rating measures which bears the risk of an under- or overestimation of symptoms. Moreover, even if psychoactive medication was adjusted for, an influence of anxiolytic medication on study outcomes cannot completely be ruled out.

5. Conclusion

A 12-week guided exercise intervention was associated with reduced symptoms of anxiety in primary care patients with anxiety syndromes. There was a significant intensity trend for increase in the proportion of patients with improved anxiety symptoms as compared to controls. The treatment effect of exercise was similar for depressive symptoms. These findings strengthen the view that physical exercise represents an effective treatment and should be more frequently made available for persons with anxiety issues within primary care. Exercise has few side effects, is inexpensive and overall beneficial for general somatic health. Future trials could address the use of guided exercise in specific anxiety disorders, compare outcomes in acute and chronic conditions and further evaluate the optimal intensity of exercise in decreasing anxiety and depressive symptoms in patients with anxiety disorders.

Author statement

Due to the sensitive nature of the questions asked in this study, survey respondents were assured raw data would remain confidential and would not be shared.

Data not available / The data that has been used is confidential

CRediT authorship contribution statement

Malin Henriksson: Methodology, Software, Formal analysis, Investigation, Data curation, Writing – original draft. **Alexander Wall:** Methodology, Software, Formal analysis, Data curation, Writing – review & editing. **Jenny Nyberg:** Conceptualization, Methodology, Writing – review & editing, Supervision. **Martin Adiels:** Methodology, Software, Formal analysis. **Karin Lundin:** Investigation, Writing – review & editing. **Ylva Bergh:** Investigation, Writing – review & editing. **Robert Eggertsen:** Writing – review & editing, Supervision. **Louise Danielsson:** Conceptualization, Writing – review & editing. **H. Georg Kuhn:** Writing – review & editing, Supervision. **Maria Westerlund:** Investigation, Supervision. **N. David Åberg:** Methodology, Software, Formal analysis, Data curation, Writing – review & editing, Supervision. **Margda Waern:** Conceptualization, Writing – review & editing, Supervision, Funding acquisition. **Maria Åberg:** Conceptualization, Methodology, Validation, Investigation, Writing – review & editing, Supervision, Project administration, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

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